REMARKS

Claims 1-30 were pending in the present application. Claims 1-27 have been withdrawn and have now been canceled, without prejudice. Claims 28-30 have been presently canceled, without prejudice in favor of new claims 31-46. Accordingly, claims 31-46 will be pending upon entry of the instant amendment. Any amendment or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite prosecution of the application. No new matter has been added by virtue of the amendments. Support for the new claims can be found in the original claim set, as well as, for example, page 33, paragraph beginning at line 5, page 45, beginning at line 5 and at page 75, paragraph beginning at line 13.

Objections to the Claims

The Examiner has objected to claim 30 under 37 C.F.R. 1.75(c) as being of "improper dependent form for failing to further limit the subject matter of a previous claim." Applicants have canceled claim 30, thereby obviating the 37 C.F.R. 1.75(c) objection. Applicants believe that new claims 31-46 are not subject to similar objections. Applicants respectfully request reconsideration and withdrawal of the foregoing objection.

The Rejection of Claims 28-30 under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 28-30 are rejected under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". Specifically, claim 28 was rejected because it recites the term "either" and provides no alternative. Applicants have canceled claims 28 to 30, in favor of new claims 31 to 46, which do not recite such a term "either", thereby obviating the 35 U.S.C. §112, second paragraph rejection of claims 28-30. Therefore, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

The Rejection of Claims 28-30 under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 28-30 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants have canceled claims 28-30 in favor of new claims 31-46. New claim 31 recites: 1) that the polypeptide be at least 95% identical to the polypeptide of SEQ ID NO:2; or 2) that the polypeptide comprises a fragment of at least 400 contiguous amino acids of SEQ ID NO:2; and 3) that the polypeptide having 95% identity to SEQ ID NO:2 or the fragment of at least 400 amino acids each exhibit sulfatase activity.

In light of these presently pending claims, Applicants traverse the Examiner's rejection and argue that they were in possession of the claimed invention at the time of filing for the reasons discussed below.

Applicants have taught that biologically active polypeptide fragments used in the claimed invention may include sequences of at least 400 contiguous amino acids of SEQ ID NO:2 (see *e.g.* page 19, paragraph beginning at line 29). Likewise, Applicants have additionally taught that isolated polypeptide molecules used in the invention include polypeptide sequences which are at least 95%, or more homologous to the entire length of the polypeptide sequence shown in SEQ ID NO:2 (see *e.g.* page 33, paragraph beginning at line 5).

Applicants have taught domains within the sulfatase polypeptide which are conserved and essential for activity of the polypeptide, namely the transmembrane domain and the sulfatase domain (see *e.g.* page 9, paragraphs beginning at line 11). Having identified the regions necessary for activity, Applicants have taught which regions of the polypeptide are amenable to alterations as well as those which are not amenable to alterations. For example, Applicants teach at lines 2-4 on page 19 that "[a]mino acid residues that are conserved among the polypeptides of the present invention, *e.g.*, those present in the sulfatase domain, are predicted to be particularly non-amenable to alteration." Applicants have also provided an example of a specific fragment comprising 429 contiguous amino acids of SEQ ID NO:2 which exhibits the sulfatase activity, namely the sulfatase family domain located at about residues 44-472 of SEQ ID NO:2 (see *e.g.* paragraph beginning at line 18 on page 9).

Additionally, the specification teaches one how to generate functional variants by performing conservative substitutions within the polypeptide used in the claimed invention. As

defined in the paragraph beginning at line 5 on page 20, "A conservative amino acid substitution is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." The Applicants have also defined which of the amino acids have similar side chains, thereby providing a skilled artisan the necessary tools to generate functional variants of the polypeptide used in the claimed invention.

Finally, Applicants have provided teachings for one of skill in the art to be able to perform assays to determine whether or not specific sequences have the desired sulfatase activity. For example, as taught on page 31 of the specification, "[a] 22437 polypeptide has one of the following characteristics: (1) it catalyzes hydrolysis of sulfate ester bonds; (2) it modulates extracellular matrix structure; (3) it modulates degradation or resorption of extracellular matrix; (4) it modulates interaction of a cell with an extracellular matrix; (5) it modulates movement of a cell into or through an extracellular matrix; (6) it modulates the sulfation state of a hormone; (7) it modulates a hormonally-mediated physiological response; (8) it modulates tumor cell invasivity; (9) it modulates tumor cell metastasis; (10) it modulates neuron growth or extension; (11) it modulates synapse formation" among others. Based on these activities, one can perform assays on specific sequences to determine whether or not such sequences have the desired biological activities. Such assays include, for example, 1) assays which monitor the hydrolysis of sulfate ester bonds; 2) assays which monitor neuron growth or extension; or 3) assays which monitor the movement of a cell into or through an extracellular matrix. Performing such assays to determine whether or not a fragment or a variant of the sequence used in the claimed invention has the desired properties would not constitute undue experimentation.

Therefore, by having provided the full length sequence of the polypeptide used in the claimed invention, a functional fragment having the desired activity and an enabling disclosure for obtaining other such functional sequences, Applicants have provided the necessary teachings to demonstrate that they were in possession of the claimed invention at the time of filing. Applicants, therefore, respectfully request reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph rejection over claims 28-30.

The Rejection of Claims 28-30 under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 28-30 are rejected under 35 U.S.C. § 112, first paragraph, as "failing to comply with the enablement requirement." Specifically, the Examiner states that "Claims 28-30 are very broad, encompassing methods wherein binding of generally any type of compound is tested for binding to a broad range of highly variant polypeptides, a major portion of which have not been described, and, therefore, also not characterized by the instant specification."

Applicants have canceled claims 28-30 in favor of new claims 31-46. New claim 31 recites: 1) that the polypeptide be at least 95% identical to the polypeptide of SEQ ID NO:2; or 2) that the polypeptide comprises a fragment comprising at least 400 contiguous amino acids of SEQ ID NO:2; and 3) that the polypeptide having 95% identity to SEQ ID NO:2 or the fragment of at least 400 contiguous amino acids each exhibit sulfatase activity.

As discussed above, Applicants have provided descriptions and teachings for every element recited in the claims. The Applicants submit that one of skill in the art would be equipped to carry out the presently claimed subject matter.

Contrary to the Examiner's assertion, the specification not only provides the sequence of the polypeptide used in the claimed invention (SEQ ID NO:2), but also provides a fragment that falls within the scope of the presently pending claims, namely the sulfatase domain, as well as extensive teachings as discussed above, to obtain other functionally active fragments or functionally active variants which fall within the scope of the presently pending claims. Therefore, contrary to the Examiner's assertion, Applicants have provided all of the necessary teachings to enable one of skill in the art to carry out the invention using fully characterized 95% variants of SEQ ID NO:2 having sulfatase activity and fragments of at least 400 contiguous amino acids of SEQ ID NO:2 having sulfatase activity, without undue experimentation.

The Examiner additionally asserts that the claimed methods are not enabled because a binding compound may not exhibit effect on activity.

New claims 31 and 39 recite: 1) that the compound to be tested and the sample comprising the polypeptide be combined under conditions suitable for detecting a sulfatase activity; 2) that the ability of the compound to modulate the sulfatase activity be assessed; and 3) that a compound capable of modulating the sulfatase activity be selected. As newly pending

claims 31 and 39 no longer rely on binding of the test compound to the polypeptide of the invention, Applicants believe the present amendments address the Examiner's concerns.

The Examiner additionally asserts that the claimed methods are not enabled because she does not believe that identified compounds would have the desired effect. Applicants respectfully traverse.

As described above, the presently pending claims recite: 1) that the compound to be tested and the sample comprising the polypeptide be combined under conditions suitable for detecting a sulfatase activity; 2) that the ability of the compound to modulate the sulfatase activity be assessed; and 3) that a compound capable of modulating the sulfatase activity be selected.

In light of these presently pending claims, Applicants submit the specification provides all of the necessary teachings to enable one of skill in the art to carry out the claimed invention for the reasons discussed below.

Applicants have taught that compounds, or candidate compounds, such as, for example, small molecules and peptides, can be screened using various types of assays in order to identify compounds which bind to or modulate the activity of the polypeptide of the invention or a fragment thereof (see, for example, page 45, beginning at line 5). The teachings of the specification include, for example, cell based assays in which a polypeptide, or fragment thereof, is contacted with a test compound and the ability of the test compound to bind to the polypeptide or the ability of the test compound to modulate the activity of the polypeptide are assessed. Likewise, Applicants have also taught cell-free assays, in which soluble and/or membrane bound forms of isolated polypeptides or fragments thereof may be used for the identification of compounds that have the ability to bind to the polypeptide or the ability to modulate the activity of the polypeptide. As taught by Applicants, assessing the ability of the test compound to bind to the polypeptide or assessing the ability of the test compound to modulate the sulfatase activity of the polypeptide can be achieved by a number of ways, such as, for example, the coupling of a test compound with a label, such as a radiolabel or an enzymatic label. Once labeled, an assay may be configured to either detect the label or to determine enzymatic activity (i.e. conversion of substrate to product) in order to determine if binding has occurred or if the compound has the ability to modulate the activity of the polypeptide. Applicants have additionally taught methods

of performing assays without labeling any of the components of the assay by using, for example, a microphysiometer, surface plasmon resonance (SPR) or real-time biomolecular interaction analysis (see *e.g.* pages 47-49, beginning at line 2 of page 47). Additionally, the assays taught by Applicants may be performed in solution or by immobilizing the test compound or the sample comprising the polypeptide of the invention to a solid support (see *e.g.* pages 49-50, beginning at line 3 of page 49).

Applicants have therefore provided sufficient teachings and exemplifications for screening assays which are commensurate in scope with the presently pending claims. The steps recited in the claims would enable one of skill in the art to identify candidate compounds for modulating a proliferative disorder, as only those candidate compounds which are assessed as being capable of modulating a sulfatase activity of the polypeptide or fragment thereof are selected. If no candidate compound successfully modulates the sulfatase activity of the polypeptide, then no candidate compound will be selected. Applicants respectfully disagree with the Examiner's assertion that "a differential level of expression of these nucleic acids would not predictably correlate with the modulation of any of the specifically claimed phenomena". As acknowledged by the Examiner, increased expression of a polypeptide of the invention in a diseased tissue or cell as compared to the level of expression of the polypeptide under normal physiological conditions is indicative that the polypeptide is either involved in the regulation of the disease phenomena or is responding to the disease state. Regardless of the mechanism in which the polypeptide is involved, if one of skill in the art is able to identify candidate compounds which have been selected based on their ability to modulate the activity of the polypeptide, such candidate compounds may be capable of modulating a proliferative disorder by either 1) increasing the polypeptide's activity (which may be useful if the polypeptide is responding to the disease state); or 2) decreasing the polypeptide's activity (which may be useful if the polypeptide is involved in the regulation of the proliferative disorder).

In light of the teachings and exemplifications provided in the present application, one of skill in the art could carry out the claimed methods without undue experimentation. Therefore, contrary to the Examiner's assertions, Applicants have provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of newly added claims 31-46. Therefore, Applicants respectfully

request reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph rejection over claims 28-30.

CONCLUSIONS

In view of the amendments and remarks made herein, Applicants respectfully submit that the objections and rejections presented by the Examiner are now overcome and that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is believed that this paper is being filed timely and that a two month extension of time is required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

March 29, 2004

MILLENNIUM PHARMACEUTICALS, INC.

By _____

Mario Cloutier
Limited Recognition Under 37 C.F.R. §10.9(b)
40 Lansdowne Street
Cambridge, MA 02139
Telephone - 617-577-3522
Facsimile - 617-551-8820